Self-renewal induced efficiently, safely, and effective therapeutically with one regulatable gene in a human somatic progenitor cell.

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Public Summary:
In the field of induced potency and fate reprogramming, it remains unclear what the best starting cell might be and to what extent a cell need be transported back to a more primitive state for translational purposes. Reprogramming a committed cell back to pluripotence to then instruct it toward a particular specialized cell type is demanding and may increase risks of neoplasia and undesired cell types. Precursor/progenitor cells from the organ of therapeutic concern typically lack only one critical attribute—the capacity for sustained self-renewal. We speculated that this could be induced in a regulatable manner such that cells proliferate only in vitro and differentiate in vivo without the need for promoting pluripotence or specifying lineage identity. As proof-of-concept, we generated and tested the efficiency, safety, engraftability, and therapeutic utility of “induced conditional self-renewing progenitor (ICSP) cells” derived from the human central nervous system (CNS); we conditionally induced self-renewal efficiently within neural progenitors solely by introducing v-myc tightly regulated by a tetracycline (Tet)-on gene expression system. Tet in the culture medium activated myc transcription and translation, allowing efficient expansion of homogeneous, clonal, karyotypically normal human CNS precursors ex vivo; in vivo, where Tet was absent, myc was not expressed, and self-renewal was entirely inactivated (as was tumorigenic potential). Cell proliferation ceased, and differentiation into electrophysiologically active neurons and other CNS cell types in vivo ensued upon transplantation into rats, both during development and after adult injury—with functional improvement and without neoplasia, overgrowth, deformation, emergence of non-neural cell types, phenotypic or genomic instability, or need for immunosuppression. This strategy of inducing self-renewal might be applied to progenitors from other organs and may prove to be a safe, effective, efficient, and practical method for optimizing insights gained from the ability to reprogram cells.

Scientific Abstract:
In the field of induced potency and fate reprogramming, it remains unclear what the best starting cell might be and to what extent a cell need be transported back to a more primitive state for translational purposes. Reprogramming a committed cell back to pluripotence to then instruct it toward a particular specialized cell type is demanding and may increase risks of neoplasia and undesired cell types. Precursor/progenitor cells from the organ of therapeutic concern typically lack only one critical attribute-the capacity for sustained self-renewal. We speculated that this could be induced in a regulatable manner such that cells proliferate only in vitro and differentiate in vivo without the need for promoting pluripotence or specifying lineage identity. As proof-of-concept, we generated and tested the efficiency, safety, engraftability, and therapeutic utility of "induced conditional self-renewing progenitor (ICSP) cells" derived from the human central nervous system (CNS); we conditionally induced self-renewal efficiently within neural progenitors solely by introducing v-myc tightly regulated by a tetracycline (Tet)-on gene expression system. Tet in the culture medium activated myc transcription and translation, allowing efficient expansion of homogeneous, clonal, karyotypically normal human CNS precursors ex vivo; in vivo, where Tet was absent, myc was not expressed, and self-renewal was entirely inactivated (as was tumorigenic potential). Cell proliferation ceased, and differentiation into electrophysiologically active neurons and other CNS cell types in vivo ensued upon transplantation into rats, both during development and after adult injury-with functional improvement and without neoplasia, overgrowth, deformation, emergence of non-neural cell types, phenotypic or genomic instability, or need for immunosuppression. This strategy of inducing self-renewal might be applied to progenitors from other organs and may prove to be a safe, effective, efficient, and practical method for optimizing insights gained from the ability to reprogram cells.

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